Age-related diseases

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Age-related diseases in people

[Graph showing the percentage of people with various age-related diseases over different age groups.]
Ageing and an accessible organ: the eye

- Nuclear sclerosis
- Atrophy and retinoschisis, peripheral retina
- ↓ rod cells (30% in aged humans)
- Vitreal liquefaction
- Loss of elasticity, lens (presbyopia)
- Microcystoid degeneration
- Hyalinization, ciliary body
- Asteroid hyalinosis
- ↑ intraocular pressure
- Arcus senilis, cornea
- ↓ contractility, iris muscles
- Drusen formation
Age-related illness in old cats and dogs

**Dogs**
- Ocular (multiple)
- Neoplasia
- Deafness
- Joint disease
- Cortical atrophy
- Hyperplasia:
  - Liver
  - Pancreas
  - Spleen
  - Prostate

**Cats**
- Ocular
- Neoplasia
- Hyperplasia:
  - Thyroid
  - Pancreas
- Amyloidosis of islets
- End-stage renal disease

Age-related organ changes in dogs

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Biological theories of ageing

- Senescence genes
- Mutation-accumulation
- Pleiotropic genes
- Disposable soma

Ageing and body mass

![Graph showing the relationship between aging and body mass with age in years on the x-axis and mass in grams on the y-axis. The equation $y = 3.5x^{0.56}$ with $R^2 = 0.340$ is displayed.]

Exceptions: bats, lizards and avian species

- **Rougheye rockfish** (Sebastes aleutianus) 205 years
- **Painted turtle** (Chrysemys picta) 61 years
- **Ocean quahog** (Arctica islandica) 400 years
- **Great Basin Bristlecone pine** (Pinus longaeva) 4,718 years
- **Red sea urchin** (Strongylocentrotus franciscanus) 200 years
- **Blanding’s turtle** (Emydoidea blandingii) 77 years

Species with ‘negligible’ senescence

**Time takes its toll**

Senescence: the collection of changes that render organisms progressively more likely to die

- endogenous factors $\rightarrow$ **Cell** $\leftarrow$ exogenous factors
  - (cellular senescence)
  - (wear and tear)
Endogenous factors

- Senescence genes:
  - Limited evidence
  - Probably little selection pressure for senescence genes in free-ranging populations, since they die young
- Genes causing (or reacting to) slowly progressive deleterious effects
  - Makes evolutionary sense – little selection pressure against
  - ↓ expression, electron transport chain genes
  - ↑ expression, cell cycle inhibitors
- ?Genes beneficial in peak reproductive years are detrimental in later life
- Telomere shortening and mitotic clock
  - Progressive shortening of telomeres at ends of chromosomes after each division
  - When too short → apoptosis, DNA-damage response, and damaged chromosomes

Telomeres and DNA damage

Ageing in cell culture

Normal differentiated diploid cells lose ability to divide after ~50 cell divisions in vitro – Hayflick phenomenon
Cellular ageing

- Functional changes in cells over time
  - ↓ oxidative phosphorylation by mitochondria
  - ↓ DNA and RNA synthesis of structural and enzymatic proteins and cellular receptors
  - ↓ capacity to repair DNA damage
  - ↓ uptake of nutrients
- Morphological changes in cells over time
  - ↓ accumulation of ageing pigment (lipofuscin)
  - ↓ vacuolated and pleomorphic mitochondria
  - ↓ r-ER
  - ↓ irregular and lobed nucleus

Exogenous factors

- Cumulative effect of stressors, esp. in permanent cell populations
  - Oxidative stress:
    - Nuclear and mitochondrial DNA:
      - 10^7 molecules ROS/mitochondrion/day
    - No protective histones
    - Membrane damage
    - Inhibition of housekeeping genes
    - Increased formation of stress proteins
    - Formation of insoluble denatured protein aggregates
    - "Chaperonopathies"
  - Age-related glycosylation
  - Protein (esp. enzymatic) changes

Ageing and the brain
Fibrosis, meninges

Cholesteatoma

Age-related changes in brain and associated structures

- Vacuolation of white matter
- Neuronal vacuolation
- Lipofuscin accumulation
- Beta-amyloid accumulation
- Neuroaxonal dystrophy
- Osseous metaplasia of meninges
- Mineralized blood vessels
Two morphological changes of AD

Extracellular plaques
Intracellular tangles

Amyloid hypothesis of AD

Endogenous toxin
Aβ generated from amyloid precursor protein

Amyloid in Alzheimer’s disease

- beta-amyloid (Aβ) peptide
- Mutations in APP = early-onset AD
- All known mutations of APP increase production of Aβ
- Trisomy 21 (Down's syndrome) children have 3 copies of gene for APP → AD in 3rd and 4th decade
- Aβ neurotoxic in vitro, leading to cell death
- Transgenic mice over-expressing human amyloid precursor protein have:
  - Neuritic plaques
  - Amyloid deposition
  - Learning/memory deficits
- Anti-amyloid antibodies in humans in AD ameliorate disease
- Other factors: apolipoprotein E4 genes and AD by 85 years
  - No gene: risk of AD = 9 – 25%
  - One allele: risk of AD = 25 – 60%
  - Two alleles (2% of population): risk of AD = 50 – 90%
Degenerative joint disease

- “Osteoarthritis” “DJD”
- Various causes, including age-related
- Wear of articular cartilage, with complications:
  - Induction of inflammation esp. in synovium by secretion by chondrocytes of inflammatory mediators
  - Chondromalacia
  - Erosion/fibrillation
  - Ulceration
  - Eburnation of subchondral bone
  - Abnormalities in joint capsule

[Diagram of osteoarthritis with various causes and consequences]

Osteoarthritis

Healthy knee joint
Hypertrophy and spurring of bone and erosion of cartilage

[Images of healthy knee joint and osteoarthritis knee]
Degenerative disk disease

- Age-related in many species:
  - Esp. dog, pig, horse, human
- Mechanical factors, including conformation
- Change in intervertebral disks:
  - Nucleus pulposus:
    - ↓Water and proteoglycans; ↑collagen; ↑calcium
  - Annulus fibrosus
    - Degeneration (loss of strength)
- Sequelae:
  - Compression of nerves, spinal cords and/or joint instability

Intervertebral disc disease

- Prolapse of nucleus
- Extrusion of nuclear contents
Age-related changes: skin

- Epidermal thinning
  - Number of cell layers unchanged
- Melanocytes ↓
  - Hypertrophy of remaining melanocytes
  - Lentigo formation
- Dermal elastosis ↓
- Sebum production by sebaceous cells ↓
- Increased fragility of dermal blood vessels
  - Bruising and cherry angiomas
- Miscellaneous benign growths
  - Skin tags

Age-related change: blood vessels, heart and connective tissue

- Connective tissue and a loss of resilience:
  - Blood vessels:
    - Basement membrane thickening in capillaries
    - Altered connective tissue in arteries and veins
    - Atherosclerosis
  - Heart:
    - Changes in chamber size (↑left atrium; ↓left ventricle)
    - Valvular degeneration:
      - Fibrosis/calcification (human)
      - Buckling of leaflets
      - Myxoid change (dog)
    - Osseous metaplasia
    - Cell loss, fibrosis and fat in SA node and conduction system
Endocardiosis

Age-related changes: immune system

- Thymic atrophy
- ↑ risk of autoimmune disease
- ↓ wound healing
  - Connective tissue component also
- ↓ immunological responsiveness:
  - Reduced immunological surveillance for neoplastic cells
  - Less effective ability to fight infection

Take home on age-associated lesions

- Biological function of ageing subject to debate
- Old age is not a disease
  - But associated with a range of disorders, most driven by genetic and environmental factors
- Spectrum of age-related changes is species- and in some cases breed-dependant
  - E.g., CNS, endocrine system, bones/joints
- Gene-array technology allows better definition of altered expression in genes
  - Multiple genes involved. Both up- and down-regulation
- Some age-related degenerations can be arrested (e.g., macular degeneration) with understanding of pathophysiology